ORIGINAL ARTICLE

Dopamine versus dobutamine in very low birthweight infants: endocrine effects

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Objectives: To compare the endocrine effects of dopamine and dobutamine in hypotensive very low birthweight (VLBW) infants.

Design: Non-blinded randomised prospective trial.

Setting: Level III neonatal intensive care unit.

Patients: 35 hypotensive VLBW infants who did not respond to volume loading, assigned to receive dopamine or dobutamine.

Measurements: Haemodynamic variables and serum levels of thyroid stimulating hormone (TSH), total thyroxine (T_4), prolactin (PRL) and growth hormone were assessed during the first 72 h of treatment and the first 72 h after stopping treatment.

Results: Demographic and clinical data did not significantly differ between the two groups. Necessary cumulative and mean drug doses and maximum infusion required to normalise blood pressure were significantly higher in the dobutamine than in the dopamine group ($p < 0.01$). Suppression of TSH, T_4 and PRL was observed in dopamine-treated newborns from 12 h of treatment onwards, whereas levels of growth hormone reduced significantly only at 12 h and 36 h of treatment ($p < 0.01$). TSH, T_4 and PRL rebound was observed from the first day onwards after stopping dopamine. Dobutamine administration did not alter the profile of any of the hormones and no rebound was observed after stopping treatment.

Conclusion: Dopamine and dobutamine both increase the systemic blood pressure, though dopamine is more effective. Dopamine reduces serum levels of TSH, T_4 and PRL in VLBW infants but such suppression is quickly reversed after treatment is stopped. Further research is required to assess if short-term iatrogenic pituitary suppression has longer-term consequences.

About 20% of very low birthweight (VLBW) infants in neonatal intensive care units become hypotensive within 24 h of admission.¹ Hypotension is a major risk factor for periventricular-intraventricular haemorrhage and poor long-term neurodevelopmental outcome,^{2–4} probably because of the low cerebral perfusion pressure and blood flow.^{5–7} Therefore hypotension is usually treated with volume expansion⁸ and inotropic agents,^{9–13} mostly dopamine and dobutamine.

Treatment with dopamine is more successful than with dobutamine.¹⁴ However, dopamine suppresses anterior pituitary function in VLBW infants^{15–20} and treatment is associated with hypothyroxinaemia of prematurity¹⁵ and low levels of prolactin (PRL).¹⁶

It has been shown that dobutamine treatment induces a small but important decrease in levels of thyroid stimulating hormone (TSH) in adults through unknown mechanisms.^{21, 22} It is currently not known whether dobutamine has similar effects in VLBW infants. Such hormonal suppression would be of great relevance because decreased thyroid function and hypoprolactinaemia are associated with worse neurodevelopmental²³ and clinical outcomes, respectively.²⁴

The aim of the present study was to compare efficacy and endocrine effects of dopamine and dobutamine in hypotensive VLBW infants.

PATIENTS AND METHODS

We conducted a prospective, randomised study in hypotensive VLBW infants weighing <1500 g born between July 2003 and June 2005 at the level III maternity hospital at Careggi, Florence, Italy. The exclusion criteria were: inherited metabolic endocrine diseases; major congenital abnormalities; shock requiring immediate treatment in delivery room; treatment

with glucocorticoids or dopamine antagonists; and ascertained or presumed pituitary or thyroidal disorders in either the newborn or the mother. The institutional review board approved the study, and written informed consent was obtained from one parent.

Hypotension was defined as mean arterial pressure (MAP) <25 mm Hg, 30 mm Hg and 32 mm Hg for birth weight of <750 g, 750–1250 g and 1250–1500 g, respectively; the blood pressure was measured twice with an interval of 30 minutes between the two recordings.² Hypotensive newborns were given isotonic saline, 10 ml/kg, by slow intravenous infusion. Those newborns who remained hypotensive after two doses of crystalloid were allocated to receive dopamine or dobutamine. The newborns received dopamine (group A) if they were enrolled in the study on odd days and dobutamine (group B) if they were enrolled on even days. Drug infusion was started at 4 $\mu\text{g/kg/min}$ and the dose increased by 2 $\mu\text{g/kg/min}$ in a step-wise fashion until either the MAP normalised or a maximal dose of 20 $\mu\text{g/kg/min}$ was reached. If the hypotension persisted after giving the maximum dose of 20 $\mu\text{g/kg/min}$, the other inotrope was added.

Heart rate, MAP and oxygen requirement were evaluated at 0, 2, 4, 8, 12, 18, 24, 48 and 72 h. Serum sodium, potassium and chloride were measured at 12, 18, 24, 48 and 72 h. Creatinine, fluid intake and mean urine output were measured daily for the first three days. All these measurements were repeated once a day in the first three days after cessation of inotropic treatment. The newborns were nursed in a thermoneutral environment, and fluid intake was started on average at 50 ml/kg/day on the

Abbreviations: MAP, mean arterial pressure; PRL, prolactin; T_4 , total thyroxine; TSH, thyroid stimulating hormone; VLBW, very low birth weight

Table 1 Demographic and clinical data of the two study groups

	Group A (dopamine)	Group B (dobutamine)	p Value
Newborns, n	18	17	
Male, n (%)	9 (50.0)	10 (58.8)	0.613
Gestational age (days), mean (SD)	196.2 (14.6)	193.1 (15.4)	0.649
Birthweight (g), mean (SD)	1014 (166)	995 (257)	0.843
Caesarean section, n (%)	13 (72.2)	14 (82.4)	0.490
Prenatal steroids, n (%)	14 (77.8)	14 (82.4)	0.744
Apgar score (5 min), mean (SD)	7.0 (1.4)	7.5 (0.7)	0.886
Crib score, mean (SD)	5.0 (2.1)	5.2 (2.9)	0.864
Survivors, n (%)	18 (100)	17 (100)	1.000
Infant respiratory distress syndrome, n (%)	18 (100)	16 (94.1)	0.311
Surfactant therapy, n (%)	15 (83.3)	14 (82.4)	0.941
Sepsis, n (%)	5 (27.8)	4 (23.6)	0.782
Patent ductus arteriosus, n (%)	9 (50.0)	8 (47.1)	0.867
Bronchopulmonary dysplasia*, n (%)	4 (22.2)	4 (23.6)	0.929
Retinopathy of prematurity†, n (%)	4 (22.2)	3 (17.6)	0.744
Intraventricular haemorrhage‡, n (%)	3 (16.7)	4 (23.6)	0.624
Necrotising enterocolitis§, n (%)	0	0	1.000

*Oxygen requirement at 36 weeks' postmenstrual age.

†IIA, IIB, IIIA and IIIB of modified Bell's stages²⁶; ‡Grades III–IV; §Grades III–IV.

first day of life and then increased depending on the postnatal age and serum level of sodium. Minimal enteral feeding was usually started on the first day of life. Arterial blood pressure was monitored with a non-invasive oscillometric blood pressure monitor (Symphony N-3100, Nellcor Puritan Bennett, Pleasanton, California, USA) every 15 min from birth. The accuracy of measurement of this monitor is ± 3 mm Hg.

To study endocrine profiles, we obtained dried blood on filter paper by heel puncture every 12 h for the first 72 h, 60 min after feeding. The 0 sample was taken before starting inotropic treatment. These measurements were repeated once a day for three days after stopping treatment. None of our newborns was treated with iodine-containing contrast media or disinfectants. Hormone assays were done at the Laboratory of Inborn Errors of Metabolism, University of Florence. TSH, T_4 , PRL and growth hormone were measured with commercial enzyme-linked immunosorbent assay kits (AutoDelfia Neonatal hTSH Ultra, T_4 , Prolactin and hGH, Wallac OY, Turku, Finland) using the AutoDelfia spectrophotometer (Wallac 1235, Turku, Finland). Measurements by time-resolved fluoroimmunoassay kit are correlated with radioimmunoassay.²⁵

Statistical analysis

We first analysed the group variables using analysis of variance (threshold $p = 0.05$). Where necessary, the analysis of variance for repeated measurements was carried out. Where significant differences in a variable were found, the groups were compared using Student's *t* test (threshold $p = 0.01$).

RESULTS

A total of 486 (283 VLBW) newborns were admitted to our eight-bed NICU during the study period. Of these, 84 (28 VLBW) were transferred to other hospitals because of lack of beds or surgical problems. Eight newborns with extremely low birthweight and gestational age died during the first hours of life. Thus from 247 VLBW newborns, 53 hypotensive newborns were enrolled in the study. One hypotensive newborn, whose mother was being given L-T4 was excluded. In two cases, consent was not obtained or the investigators could not collect blood properly. Thirty-five (66%) newborns remained hypotensive after two doses of isotonic saline solution.

Table 2 Haemodynamic and metabolic status at study entry and inotropic infusions during the study.

	Group A (dopamine)	Group B (dobutamine)	p Value
Newborns, n	18	17	
Study entry			
Age (hours of life)	4.6 (2.0)	4.1 (1.6)	0.318
Systolic arterial pressure (mmHg)	43.8 (2.1)	42.9 (2.3)	0.376
Diastolic arterial pressure (mmHg)	23.2 (1.4)	22.1 (1.8)	0.143
Mean arterial pressure (mmHg)	28.7 (1.6)	28.7 (0.9)	1.000
Heart rate (bpm)	153.4 (7.8)	149.5 (11.2)	0.427
Maximum fractional inspired O_2 (%)	28.8 (8.8)	29.3 (8.4)	0.449
pH ($-\log[H^+]$)	7.311 (0.09)	7.314 (0.08)	0.469
pCO ₂ (mmHg)	43.0 (11.4)	45.3 (8.8)	0.309
pO ₂ (mmHg)	74.8 (9.4)	72.3 (11.5)	0.297
HCO ₃ ⁻ (mmol/l)	19.1 (2.5)	18.8 (2.8)	0.411
Anion gap (mmol/l)	4.3 (3.5)	4.5 (3.5)	0.452
During the study			
Duration of infusion (h)	71.4 (18.9)	73.6 (14.3)	0.386
Cumulative dose of infusion (μ g/kg)	21440 (6256)	27704 (6709)	<0.01
Mean dose of infusion (μ g/kg/day)	5.0 (0.5)	6.2 (0.8)	<0.01
Maximum infusion rate (μ g/kg/min)	7.4 (2.1)	11.6 (4.9)	<0.01

Values are mean (SD).

We did not find significant differences between the groups with regard to demographic data, mortality and main neonatal morbidities before discharge (table 1) or the haemodynamic and metabolic profile at study entry (table 2). The necessary cumulative and mean administered dose, and the maximum infusion rate required to normalise MAP were significantly higher for the dobutamine group than the dopamine group (table 2; $p < 0.01$ for all). In the two newborns who remained hypotensive despite being given the maximal dobutamine dose, dopamine was added at 8 μ g/kg/min and 10 μ g/kg/min. We did not find any significant differences between the two groups with regard to heart rate, oxygen requirement, fluid intake and mean urine output during the treatment, and serum levels of sodium, potassium, chloride and creatinine.

At study entry, serum levels of TSH, total thyroxine (T_4), PRL and growth hormone were similar in the two groups. From 12 h onwards, serum levels of TSH, T_4 and PRL were significantly lower in group A ($p < 0.01$), whereas growth hormone was significantly lower only at 12 and 36 h (fig 1; $p < 0.01$).

The levels of TSH, T_4 and PRL increased briskly after stopping dopamine treatment. TSH increased from a mean (SD) 0.3 (0.2) mU/l when the treatment was stopped to 1.3 (0.8) mU/l ($p < 0.01$), 1.5 (1.1) mU/l ($p < 0.01$) and 1.8 (1.1) mU/l ($p < 0.01$) after 24, 48 and 72 h, respectively. T_4 increased from 20.8 (7.9) nmol/l to 45.6 (7.5) nmol/l ($p < 0.01$), 50.1 (8.4) nmol/l ($p < 0.01$) and 56.3 (10.4) nmol/l ($p < 0.01$), respectively. PRL increased from 42.9 (10.4) μ g/l to 74.8 (13.5) μ g/l ($p < 0.01$), 86.6 (15.1) μ g/l ($p < 0.01$) and 114.6 (21.2) μ g/l ($p < 0.01$), respectively. We also found a mild, but not significant, increase in levels of growth hormone from 34.1 (14.8) μ g/l to 42.7 (17.0) μ g/l ($p = 0.351$), 50.6 (11.2) μ g/l ($p = 0.015$) and 52.8 (14.8) μ g/l ($p = 0.015$), respectively (fig 2A). Stopping dobutamine did not significantly affect the hormonal levels (fig 2B).

DISCUSSION

Although in the present study we did not measure systemic and organ blood flow, aggressive treatment of hypotension is widely advised to preserve adequate organ perfusion.¹⁴ The firstline

Figure 1 Three-day serum levels of (A) thyroid stimulating hormone (TSH), (B) total thyroxine (T_4), (C) prolactin (PRL) and (D) growth hormone (GH) in the two study groups (dopamine group, $n=18$; dobutamine group, $n=17$). * $p<0.01$.

treatment is volume expansion and we gave our newborns isotonic saline rather than colloids because albumin infusion had been reported to increase mortality in critically ill patients.²⁷ Only a third of hypotensive newborns in the present study responded to volume replacement, confirming that left

ventricular dysfunction and reduced vascular tone may have a central role in shocked VLBW infants.²⁸

With regard to the first aim of the study, both inotropes resulted in increase in blood pressure, but we also confirmed dopamine to be more effective.^{1, 29–34} The second aim of our study was to compare the influence of dopamine and dobutamine on the thyroid axis and on PRL and growth hormone secretion as this has not previously investigated in VLBW newborns. Previous studies have suggested that dopamine infusion suppresses PRL, TSH and T_4 secretion by acting on specific D_2 receptors.³⁵ In our study also, dopamine soon induced pituitary suppression, on the first day of treatment, with TSH decreasing in group A to 14.3%, 6.3% and 5.9% of the 0 sample at 24, 48 and 72 h of life, respectively. In contrast, TSH levels fell quickly in group B as expected physiologically,^{36–37} and remained approximately three to four times higher than in group A (fig 1A). However, TSH levels in group B infants were lower than in newborns not receiving inotropes,¹⁶ suggesting a possible mild dobutamine-induced TSH suppression. Similarly, T_4 and PRL profiles differed significantly between the two groups. In group A, T_4 levels decreased to 39.1% of the initial values at 24 h, and to 34.1% at 48 and 72 h, three times lower than in group B (fig 1B). PRL levels in group A decreased to 54.0%, 46.8% and 51.6% at 24, 48 and 72 h, respectively, about two times lower than in group B (fig 1C). Levels of growth hormone were also lower in group A but the difference was significant only at 12 and 36 h (fig 1D). On the contrary, dobutamine administration did not alter T_4 , PRL and growth hormone production, suggesting that the therapeutic concentrations affect different receptors.³⁸ Compared with previous studies,^{15, 16, 36–37} our dopamine-treated infants had lower levels of TSH, T_4 , PRL and growth hormone, probably because the dopamine cumulative dose was considerably higher.

The high pulsatility of growth hormone secretion means that for a proper profile assessment sampling should be done every 15–20 min, but we did not do this because it would have meant shortening the time intervals in our study. As the levels of growth hormone rise after feeding,³⁹ blood was collected 1 h after feeding. However, the timing of blood sampling was probably not relevant in our study population because only small meals were given in the first days of life. Even though we did not measure the levels of active thyroid hormones, T_4 was considerably low in our dopamine-treated newborns. Crucially,

Figure 2 Serum levels of thyroid stimulating hormone (TSH), total thyroxine (T_4), prolactin (PRL) and growth hormone (GH) after stopping (A) dopamine or (B) dobutamine treatment, expressed as percentage of values on the day before the drug was stopped. Numbers of neonates studied at each time point are given in parenthesis. * $p<0.01$.

What is already known on this topic

- Hypotension in preterm infants is a major risk factor for periventricular-intraventricular haemorrhage and poor long-term neurodevelopmental outcome.
- Dopamine treatment is more successful than dobutamine but is associated with hypothyroxinaemia of prematurity and low levels of prolactin.
- It is not known whether dobutamine has similar effects in very low birthweight infants.

What this study adds

- Dopamine and dobutamine are both effective in the treatment of hypotensive very low birthweight infants who do not respond to volume loading, with dopamine being more effective.
- Dopamine causes a marked reduction in thyroid stimulating hormone, T_4 and prolactin levels, and there is significant hormonal rebound 24 h after stopping treatment.

thyroid homeostasis controls important functions such as surfactant production, gastrointestinal motility and cardiac activity,^{40–41} and decreased thyroid function in preterm infants is associated with increased risk of unfavourable neurodevelopmental outcome.^{23–42} However, thyroid hormone treatment in very preterm infants has not been found to have any clinical or long-term benefit.⁴³ Also, hypoprolactinaemia is associated with worse clinical outcome²⁴ probably because PRL takes part in immune regulation in critical patients.⁴⁴ At present, however, there are no data on such interactions in newborns.

Hormonal rebound was significant 24 h after stopping dopamine, when TSH was at least three to four times higher than the mean value on the last day of dopamine treatment, and T_4 and PRL levels were two to three times higher. In a previous study, dopamine-induced decrease in PRL levels seemed to be markedly influenced by gestational age and birth weight, suggesting a developmental regulation of dopamine control of PRL secretion.²⁰ Despite the very low gestational age and birth weight of our study population, PRL suppression and rebound were more evident than in previous studies.^{16–20} This is probably because we gave higher doses and the treatment was of longer duration. The mean increase in growth hormone levels was non-significant, confirming that dopamine does not exert major effects on secretion of growth hormone.

In conclusion, our data confirm that dopamine and dobutamine are both effective for treating volume loading refractory hypotension in VLBW preterm infants. In contrast with dobutamine, dopamine significantly reduces the levels of TSH, T_4 and PRL. On the basis of the rapid reversal that occurred after dopamine was stopped, we can speculate that the iatrogenic pituitary suppression that is induced for a short time with dopamine infusion will probably not cause long-term injury. Caution is required mainly if dopamine is administered for a long time. We recommend adequately powered long-term follow-up studies to rule out long-term effects.

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IMAGES IN NEONATAL MEDICINE.....

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Life-threatening bleeding from thymic cysts in a newborn

Thymic enlargement is a common physiological and incidental finding on chest x rays in healthy neonates and infants. There are usually no clinical symptoms or complications, and pathological lesions in infant thymi are rare.

Figure 1 T2-weighted MRI of the thorax showing a large anterior mediastinal mass extending to the thoracic aperture and partially compressing the heart. There are some hyperdense areas within the mass, suspicious for bleeding. Pleural effusion is also present.

We report on a 5-week-old boy with recurrent respiratory distress since birth, pursed-lips breathing with prolonged duration of expiration and tachypnoea. MRI showed massive congenital thymic hyperplasia (fig 1) with huge life-threatening mediastinal bleeding from ruptured thymic cysts into the pleural spaces. Thoracotomy and complete thymectomy were carried out, and the baby was discharged from the hospital on the fourteenth postoperative day without further complications.

The differential diagnosis of anterior mediastinal masses in neonates includes lymphangioma, teratoma, lipoma, lymphofollicular hyperplasia in myasthenia gravis, thyroid enlargement, physiological reaction to breast feeding and thymic disorders.¹ Of these, thymic hyperplasia is the most common. Congenital thymic cysts are remnants of the thymopharyngeal duct.² However, haemorrhage from ruptured thymic cysts in a neonate is exceedingly rare; it may occur in haemorrhagic disease of newborns.³

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